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Free-running 3D Whole Heart Myocardial T1 Mapping with Isotropic Spatial Resolution

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ABSTRACT

Purpose: To develop a free-running (free-breathing, retrospective cardiac gating) 3D myocardial T1 mapping with isotropic spatial resolution.

Methods: The free-running sequence is inversion recovery (IR)-prepared followed by continuous 3D golden angle radial data acquisition. 1D respiratory motion signal is extracted from the k-space center of all spokes and used to bin the k-space data into different respiratory states, enabling estimation and correction of 3D translational respiratory motion, whereas cardiac motion is recorded using ECG and synchronized with data acquisition. 3D translational respiratory motion compensated T1 maps at diastole and systole were generated with 1.5mm isotropic spatial resolution with low-rank inversion and high-dimensionality patch-based undersampled reconstruction. The technique was validated against conventional methods in phantom and nine healthy subjects.

Results: Phantom results demonstrated good agreement ($R^2=0.99$) of T1 estimation with reference method. Homogeneous systolic and diastolic 3D T1 maps were reconstructed from the proposed technique. Diastolic septal T1 estimated with the proposed method ($1140\pm 36\text{ms}$) was comparable to the saturation recovery single-shot acquisition (SASHA) sequence ($1153\pm 49\text{ms}$), but was higher than the modified Look-Locker inversion recovery (MOLLI) sequence ($1037\pm 33\text{ms}$). Precision of the proposed method ($42\pm 8\text{ms}$) was comparable to MOLLI ($41\pm 7\text{ms}$) and improved with respect to SASHA ($87\pm 19\text{ms}$).

Conclusions: The proposed free-running whole heart T1 mapping method allows for reconstruction of isotropic resolution 3D T1 maps at different cardiac phases, serving as a promising tool for whole heart myocardial tissue characterization.

Keywords: myocardial T1 mapping, free-running, inversion recovery, 3D radial

INTRODUCTION

Cardiovascular magnetic resonance has been increasingly used to diagnose and monitor different cardiac diseases (1,2). Quantitative mapping of tissue parameters has demonstrated the potential to characterize subtle pathological changes of the myocardium and is especially valuable in detecting both focal and diffuse fibrosis (3,4). T1 is sensitive to the changes of myocardial tissue properties, such as fibrosis, fat and water content, and thus is considered a promising novel biomarker to characterize myocardium and assess various cardiomyopathies (5-8). In addition, extracellular volume fraction, which is important to detect diffuse myocardial fibrosis, can be estimated from native and post-contrast myocardial T1 mapping (9). Myocardial T1 mapping has been recognized as one of the most valuable quantitative mapping techniques to support diagnostic, therapeutic and prognostic decision making in ischemic and non-ischemic cardiomyopathies (4).

The Modified Look-Locker Inversion recovery (MOLLI) (10) and saturation recovery single-shot acquisition (SASHA) (11) are commonly used cardiac T1 mapping techniques. They acquire multiple images with different T1 contrasts and estimate pixel-wise T1 by fitting the acquired signal to an exponential recovery model. Respiratory and cardiac motion may result in blurring artefacts in each T1-weighted image and can cause misalignment between different images, influencing the T1 mapping accuracy (12). Therefore, breath-holding or respiratory gating and electrocardiography (ECG) triggering are usually required during cardiac imaging. However, besides the requirement of patient compliance, a single breath-hold limits acquisition time and results in low spatial resolution and limited coverage as typically only one image is acquired per cardiac cycle (10,11). Multiple breath-holds may allow longer acquisition time, but may result in different breath-hold positions, which can lead to mis-registration artefacts and inaccuracy of T1 estimation (13). Respiratory gating has been used to limit respiratory motion during free-breathing imaging, but has low imaging efficiency and may lead to unpredictable long acquisition time (14). ECG triggering is usually used to gate the acquisition only at diastole in each cardiac cycle, which has low acquisition efficiency and can be challenging in arrhythmic patients who have shortened diastolic phase.

Recently, the magnetic resonance multitasking technique using 2D radial acquisition has been proposed for motion-resolved quantitative myocardial T1 and T2 imaging without breath-holding or ECG triggering (15,16). 2D myocardial mapping is typically performed with thick slices to avoid the influence of through-plane motion (13) and low signal-to-noise ratio (SNR).

3D acquisitions can overcome these limitations and provide whole heart coverage for comprehensive characterization of diffuse diseases of myocardium (17). However, 3D T1 mapping is technically challenging, since respiratory gating and ECG-triggering together with the requirement of whole heart coverage, may lead to very long scan time. To cover the whole heart in an acceptable scan duration, current 3D T1 mapping techniques (14,18) acquire only a few slices in the short-axis view with a slice thickness of $> 8\text{mm}$, which require complex scan planning and may suffer from partial volume effect along the slice direction.

To address the current technical challenges of myocardial T1 mapping, we propose a free-running (free-breathing, retrospective cardiac gating) 3D whole heart T1 mapping technique with high isotropic spatial resolution (1.5mm^3), which is able to provide images in any desired orientation. The proposed sequence consists of an inversion recovery (IR)-prepulse, followed by an efficient 3D golden angle radial acquisition (19) to sample the T1 relaxation curve. The k-space center is repeatedly sampled within each spoke and used to estimate 1D respiratory motion. ECG signal is recorded and synchronized with data acquisition. Respiratory binning is performed based on the estimated 1D respiratory signal, enabling estimation and correction of 3D translational respiratory motion. For the reconstruction, a recently proposed algorithm that combines dictionary-based low-rank inversion (20) and high-dimensionality 3D patch-based undersampled reconstruction (HD-PROST) (21) is used. The proposed approach allows for respiratory motion compensated 3D myocardial T1 mapping at different cardiac phases. The feasibility, accuracy and precision of the proposed technique was validated against conventional T1 mapping methods in a standardized T1 phantom and nine healthy subjects.

METHODS

Free-running 3D T1 Mapping Sequence

The proposed IR-prepared 3D radial sequence is shown in Fig.1A. IR-preparation is used to generate T1 contrast, after which a spoiled gradient-echo (SPGR) readout is performed with small flip angle (θ). Spatial-spectral pulse for selective water excitation is adopted for fat suppression. To achieve pseudo-uniform distribution of radial spokes for retrospective cardiac and respiratory binning, the continuously acquired radial spokes conform to the 3D golden angle distribution (19). Specifically, the azimuthal angle and polar angle increments ($\Delta\phi$, $\Delta\theta$) between adjacent spokes are defined as:

$$\Delta v = \text{acos}(\phi_1), \Delta \tau = 2\pi \cdot \phi_2 \quad [1]$$

where $\phi_1=0.4656$, $\phi_2=0.6823$ are the 2D golden angle means (19).

Motion Extraction and Retrospective Sorting

The flowchart of retrospective processing, including motion extraction, respiratory motion correction and data sorting for T1 mapping of a given cardiac phase is shown in Fig. 1B. Independent component analysis (ICA) was performed on the k-space center of all spokes from all coils to extract the signal component that is most relevant to the 1D superior-inferior respiratory motion. This approach has been previously validated for cardiac cine and coronary artery MRI using either radial or spiral trajectory (22,23). To extract the self-navigated respiratory signal from the k-space center, coil compression is firstly performed using principle components analysis. ICA is applied to the k-space center amplitudes from the compressed coils to obtain 5 independent components (IC). Example of the extracted ICs and the corresponding spectral power are shown in Fig. 2A, B. The harmonic corresponding to the contrast change due to IR preparation is removed from the ICs based on the IR repetition time (IRTR in Fig. 1A). Then, the IC with the highest spectral power in the respiratory frequency range (0.1-0.5Hz) is selected (IC 4 in Fig. 2A) and band-pass filtered to get the 1D respiratory signal, based on which the k-space data is binned into five equally populated respiratory phases from end-inspiration to end-expiration. An example of the estimated respiratory signal validated against the corresponding respiratory bellow signal is shown in Fig. 2C. Cardiac motion synchronization is achieved by logging the ECG time stamps, from which the temporal occurrence of each spoke relative to the most recent cardiac R-wave preceding the spoke is calculated and termed as cardiac delay.

After retrospective respiratory binning and cardiac gating, 3D translational respiratory motion is estimated via registration from the intermediate reconstruction of low-resolution respiratory bin images at diastolic cardiac phase by using central part of selected k-space data. Representative diastolic bin images of 5 respiratory motion states and the difference images with the end-expiratory bin are shown in Fig. 2D. A rectangular volume of interest for motion estimation is selected around the heart at the end-expiratory bin and propagated to other respiratory bins. Respiratory motion correction is performed by correcting the phase of the k-space data using the estimated 3D translational motion parameters. The respiratory motion

corrected k-space data can then be binned according to the cardiac delay and inversion recovery time (TI) for T1 mapping at a given cardiac phase.

Image Reconstruction

HD-PROST Algorithm

For 3D T1 mapping at a given cardiac phase, spokes for the corresponding cardiac delay and acquisition window are selected, which are then sorted into a time series of T1 contrasts according to TI and a given temporal window for each T1 frame. After data selection, the highly undersampled 3D radial data is reconstructed over multiple T1 contrasts by combining a dictionary-based low-rank inversion (20) to efficiently reduce the number of T1 contrasts to be reconstructed with a recently proposed high-dimensionality 3D patch-based undersampled reconstruction (HD-PROST), exploiting local (within a patch), non-local (between similar patches) and contrast redundancies (21). The reconstruction for the proposed technique can be formulated as the following unconstrained Lagrangian (21):

$$L(I, T, Y) = \|EI - \sqrt{D} K\|_F^2 + \lambda \sum_p \|\mathcal{T}_p\|_* + \mu \sum_p \|\mathcal{T}_p - P_p(I) - P_p(Y)\|_F^2 \quad [2]$$

where $\|\cdot\|_F$ and $\|\cdot\|_*$ denote the Frobenius norm and nuclear norm respectively; I is the compressed T1 image series to be reconstructed; $E = \sqrt{D}AU_rFS$ is the encoding operator, with S being sensitivity maps, F being Fourier Transform, U_r being the low-rank operator obtained by truncating the singular value decomposition (SVD) of a dictionary generated by Bloch simulation (20), A being the convolutional gridding operator, transforming Cartesian data back to 3D radial, and D being the non-Cartesian density compensation function; K is the undersampled data; $P_p(\cdot)$ is the patch selection operator at pixel p of a 3D multi-contrast image set. This operator selects patches on local (patch for a given pixel location and contrast), non-local (similar patches within a neighbourhood for a given contrast) and contrast (patches from all the contrasts) scales and \mathcal{T}_p is a 3D tensor built by the selected patches centered at pixel p ; T represents the denoised multi-contrast images constructed by folding and aggregating the tensors \mathcal{T}_p for each pixel p (see the step 2 below); Y is the Augmented Lagrangian multiplier; λ is the sparsity-promoting regularization parameter and μ is the penalty parameter. Equation [2] can be efficiently solved by operator-splitting via alternating direction method of multipliers (ADMM), which divides the optimization process into the following three steps:

Step 1: Joint reconstruction update

The first step is a joint reconstruction of the compressed TI image series (i.e. singular images) I by incorporating the denoised multi-contrast images T obtained at the end of step 2 as prior information:

$$L_{Joint}(I) = \underset{I}{argmin} \|EI - \sqrt{D} K\|_F^2 + \mu \|T - I - Y\|_F^2 \quad [3]$$

The above equation can be efficiently solved using the conjugate gradient (CG) algorithm.

Step 2: High-order singular value decomposition based denoising

With obtained I and Y from step 1 and step 3 separately, the second step is to minimize the following equation regarding to the high order tensor \mathcal{T}_p :

$$L_{Tensor}(\mathcal{T}_p) = \underset{\mathcal{T}_p}{argmin} \sum_p \|\mathcal{T}_p - P_p(I) - P_p(Y)\|_F^2 + \frac{\lambda}{\mu} \sum_p \|\mathcal{T}_p\|_* \quad [4]$$

The details to solve the above equation can be found in (21). Generally speaking, \mathcal{T}_p is obtained by thresholding the singular values obtained via high-order singular value decomposition of the 3D tensor built by the patches selected from the multi-contrast images. The thresholding parameter is defined by $\frac{\lambda}{\mu}$. The denoised \mathcal{T}_p is then rearranged to form the denoised image patches. This process is repeated for all the pixels in the singular images, and aggregation is then performed to generate the final denoised singular images T .

Step 3: Lagrangian multiplier update

Finally, with the optimized I and T from step 1 and step 2, the Lagrangian multiplier is updated by $Y = Y + I - T$. The above 3 steps are iteratively interleaved in the reconstruction process to improve the reconstructed image quality.

Implementation Details

The sequence was implemented on a 1.5T MRI scanner (Ingenia, Philips Healthcare, The Netherlands) for cardiac imaging. The following scan parameters were used for both phantom and in-vivo experiments: FOV = 200×200×200mm³, spatial resolution = 1.5×1.5×1.5mm³, TR/TE = 11.6ms/5.1ms, flip angle = 6°, IRTR=2200ms, number of readouts after IR=175, T_{gap} =9.5ms (minimum value allowed on the available scanner), T_{ex} =160.5ms, scan duration = 9.5min.

For the retrospective data selection for a given cardiac phase, the cardiac acquisition window was set to 186 ms, similar to the acquisition window of conventional 2D MOLLI and SASHA

imaging (10,11). The temporal window per T1 frame was also set to 186ms, resulting in ten T1 frames to be reconstructed. A dictionary-based low-rank compression (20) was performed along the T1 contrast dimension to further reduce the number of T1 frames to be reconstructed (Eq. [2]). The dictionary was generated using Bloch simulation for T1 in the range of 100ms to 3000 ms, with an increment of 1% with respect to the previous T1. The contrast of a specific TI frame is given by the average of all the radial spokes binned into the corresponding frame. The signal of each radial spoke is calculated using Bloch equation, which has been previously described for 3D radial-based carotid quantitative mapping (24,25), and is also provided in the Supporting file. The singular values by SVD of the dictionary are shown in Fig. 3A. The low-rank operator U_r in Eq. [2] was obtained by keeping the three largest singular value vectors, resulting in three singular images to be reconstructed (Fig. 3B). The first singular image, with the highest signal-to-noise ratio, was used for patch selection in the step 2 of HD-PROST (Eq. [4]).

In this study, the maximum number of CG iterations in the joint MR reconstruction (step 1) was set to 15, and the regularization parameter μ , balancing the contribution of the prior term, was empirically set to 0.01. Coil sensitivity maps were estimated by using spokes of TI larger than 1000ms and reconstructed in low resolution by using only the central half of k-space to reduce noise. The regularization parameter λ of HD-PROST was optimized by visual inspection of the reconstruction quality on one subject and used for all other dataset. For the patch-based denoising step in HD-PROST (21), the following parameters were used: patch size = $5 \times 5 \times 5$; search window = $10 \times 10 \times 10$; patch offset = 3; number of selected similar patches = 15. The number of ADMM iterations was set to 5. Example singular images after HD-PROST reconstruction are shown in Fig. 3B. T1 maps were generated by a dot product matching between the reconstructed singular images and the dictionary.

Phantom Experiments

To test the T1 mapping accuracy of the 3D T1 mapping sequence, a standardised T1 phantom (26) consisting of 9 agarose-based vials with T1 values ranging from about 250ms to 1600ms was imaged using a 28-channel cardiac coil. To obtain reference T1 values of the phantom for validation, a 2D inversion recovery spin echo (IR-SE) sequence was performed with the following imaging parameters: FOV = $140 \times 140 \text{mm}^2$, in-plane spatial resolution = $1.5 \times 1.5 \text{mm}^2$, slice thickness = 8mm, TR/TE = 10000/5.8ms, 13 TIs = 50, 100, 200, 300, 400,

500, 700, 900, 1200, 1500, 2000, 2500 and 3000ms. Standard T1 values were determined by a 3-parameter non-linear least square fitting algorithm.

For the proposed 3D radial T1 mapping sequence, the ECG signal used for the retrospective binning was generated by physiological simulation with heart rate varying between 50bpm and 70bpm during the acquisition. The acquired 3D radial data was retrospectively binned into ten T1 contrasts for a simulated diastolic phase with cardiac delay of 650ms. The phantom T1 map acquired with the 3D imaging sequence was generated using the HD-PROST reconstruction as explained above.

In vivo Experiments

The study was approved by the local institutional review board and 9 healthy subjects (5 males, 31.8 ± 3.5 years) were imaged using a 28-channel cardiac coil. All volunteers provided written informed consent before inclusion into this study. Firstly, standard breath-hold 2D cine images were acquired in the mid ventricular short-axis view with retrospective gating to 16 cardiac phases, based on which the cardiac delays for systole and diastole were determined. The T1 mapping reference consisted of the clinically adopted breath-hold 2D MOLLI (3-3-5) (27) and 2D SASHA (11) sequences which were performed in diastole. The imaging parameters of MOLLI were TR/TE = 2.6/1.3ms, flip angle = 35° , FOV = $288 \times 288 \text{ mm}^2$, in-plane resolution = $2 \times 2 \text{ mm}^2$ and slice thickness = 8.0 mm. The SASHA sequence was performed with TR/TE = 2.6/1.3 ms, flip angle = 70° and the same FOV and spatial resolution as used for MOLLI. Parallel imaging with SENSE acceleration factor of 2 in the phase-encoding direction was used in the 2D MOLLI and SASHA mapping acquisitions, resulting in a mid-diastolic acquisition window of about 187ms. MOLLI and SASHA images were acquired in the same short-axis location as the cine scan and reconstructed to an in-plane resolution of $1.5 \times 1.5 \text{ mm}^2$. The 2D T1 maps for MOLLI and SASHA were obtained by fitting the corresponding standard 3-parameter models (10,11).

The proposed free-running 3D T1 mapping sequence was also acquired in short-axis orientation covering the entire heart and centered around the slice location of the 2D MOLLI and SASHA scans. Besides diastole, T1 mapping was also reconstructed for systole using the proposed framework, considering that systolic T1 maps may find applications in patients with thin myocardium or arrhythmias (28,29).

Image Analysis

For phantom data, circular region-of-interests (ROIs) were drawn for each vial and the mean and standard deviation (SD) of T1 values were calculated for each vial. The accuracy of the proposed 3D T1 mapping technique was evaluated by comparing the estimated T1 values to the 2D IR-SE method using Pearson's linear correlation and Bland-Altman analyses.

For the analysis of in vivo images, the diastolic T1 map in the mid short-axis view that was most similar to the MOLLI and SASHA geometry was selected from the 3D T1 maps of the proposed approach for each subject. Septal ROIs with the same size were drawn for the three T1 mapping methods. The mean and SD of T1 values in the septum were measured and compared between the proposed 3D method and 2D MOLLI and SASHA separately using the Wilcoxon rank-sum test with Bonferroni Correction to evaluate the in vivo accuracy and precision.

For the analysis of 3D in vivo T1 maps, 3 slices from base, mid to apex were selected from the diastolic and systolic T1 maps. T1 values of the myocardium were measured according to the myocardial segments model defined by the American Heart Association (AHA) (30), with 6 segments in the base and middle slices and 4 segments in the apical slice. The mean T1 values were calculated for all segments to evaluate the spatial T1 distribution of the proposed method. The T1 value in each segment was compared between diastole and systole using the paired t-test. Then the diastolic and systolic T1 values for each segment were determined by averaging across all the volunteers and visualized with bull's-eye plots.

All image reconstruction and analysis were performed using MATLAB (The MathWorks, Natick, MA) on a server with a dual 16-core CPU, and 256GB RAM. Statistical analysis was carried out in GraphPad Prism 7 (La Jolla, CA). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Phantom Study

Phantom T1 maps with the proposed approach and 2D IR-SE are shown in Fig. 4A, B, and the mean and SD of T1 values of all vials are shown in Fig. 4C. The linear correlation indicates good agreement of T1 estimations between the proposed 3D technique and the 2D IR-SE reference ($R=0.99$). Bland-Altman plot demonstrates no correlation between the difference and average of T1 measurements of the two methods (Fig. 4D). Compared with 2D IR-SE, the

percentage error of the T1 measurements with the proposed approach was $1.2\pm0.7\%$, ranging from 0.3% to 2.1%.

In vivo Study

All volunteers completed the scans, and the diastolic and systolic 3D T1 maps were successfully reconstructed for each subject with recorded heart rates of 62 ± 8 bpm, ranging from 45 to 73 bpm. For reconstruction of the 3D T1 map, each ADMM iteration in HD-PROST takes about 34.9min consisting of 26.3min for the joint reconstruction step and 8.6min for the patch-based denoising step, resulting in a total reconstruction time of 174.5min with 5 ADMM iterations. T1 mapping results at diastole from a representative healthy subject are shown in Fig. 5, consisting of 8 representative short-axis slices and a reformatted long-axis slice. As can be seen, the spatial distribution of myocardium T1 was uniform over the whole left ventricle.

Diastolic T1 mapping results from another 2 subjects are shown in Fig. 6, including the mid short-axis and long-axis slices from the 3D T1 mapping approach and a middle short-axis slice from 2D MOLLI and SASHA techniques. Diastolic T1 maps reconstructed by the proposed technique were visually comparable to the reference 2D methods with improved depiction of the right ventricle. The mean and standard deviation of septal T1 derived from 2D MOLLI, 2D SASHA and the proposed 3D technique are compared in Fig. 7 for all subjects. The mean septal T1 measured with the proposed approach is 1140 ± 36 ms and is comparable to that of SASHA (1153 ± 49 ms) ($P = 0.68$), but is higher than that of MOLLI (1037 ± 33 ms) ($P < 0.01$). The SD, indicating the precision of septal T1 measurements, was 42 ± 8 ms with the proposed approach, which is much lower than the SD of SASHA (87 ± 19 ms) ($P < 0.01$) and similar to that of MOLLI (41 ± 7 ms) ($P = 0.79$).

Representative systolic and diastolic T1 maps from 2 subjects are shown in Fig. 8, where three short-axis slices (base, mid and apex) are included. The systolic T1 maps also demonstrated a uniform T1 distribution with thicker myocardium compared with diastole. The diastolic and systolic T1 values of each AHA segment are shown in the bull's-eye and box plots in Fig. 9. The comparison of T1 values in diastole and systole for all myocardium segments are summarized in Table 1. No significant differences were found between the diastolic and systolic T1 values estimated with the proposed technique in most of the AHA segments, except for the inferior segments in the apical and mid ventricular slices, and the inferoseptal segment in the basal slice, with significantly longer T1 values in diastole than in systole.

DISCUSSION

In this study, free-running 3D whole heart myocardial T1 mapping with 1.5 mm³ isotropic spatial resolution has been successfully achieved with predictable 9.5min scan time. The proposed sequence features free-breathing, retrospective cardiac gating and continuous data acquisition, so T1 maps can be compensated for 3D translational respiratory motion and reconstructed at different cardiac phases by retrospective data binning. Using combined dictionary-based low-rank inversion (20) and high-dimensionality 3D patch-based undersampled reconstruction algorithm (HD-PROST) (21) to reconstruct the highly undersampled 3D radial data, feasibility of myocardial T1 mapping was demonstrated in vivo. Myocardial T1 measurements with the proposed 3D technique were comparable to conventional breath-hold, cardiac-gated 2D MOLLI and SASHA.

In the phantom study, T1 values estimated with the proposed technique showed good accuracy for T1 ranging from 250ms to 1600ms as compared with the reference 2D IR-SE. Septal T1 values at diastole with the proposed technique were comparable to SASHA and were significantly larger than those for MOLLI, which has been reported to underestimate T1 (12). In this study, the dictionary was simulated with a linear T1 increment of 1%, resulting in 10-12ms increments in the myocardial T1 range of 1000-1200ms, which are small compared with the measured septal T1 SD (42 ± 8 ms). The precision of septal T1 was similar to MOLLI and significantly higher than SASHA. The results indicate that the proposed 3D T1 mapping technique improves accuracy compared to MOLLI and precision compared to SASHA. Therefore, the proposed technique may be a promising tool for myocardial T1 mapping with the advantages of both high accuracy and precision. In addition, with the proposed 3D high resolution T1 mapping technique, visualization of the right ventricle was improved, which may facilitate fibrosis quantification in the thin wall of the right ventricle. Nevertheless, T1 values of the thin right ventricle should be interpreted carefully, considering that there may be partial volume effects resulting from residual fat caused by the imperfection of the water selective excitation pulse.

In this study, respiratory motion was addressed by correcting the phase of k-space data using motion parameters estimated from 3D translational image registration of images acquired at different respiratory states. More sophisticated registration methods, such as affine and non-linear transforms could be considered in future work to account for more complex respiratory-induced cardiac movement. To extract reliable cardiac trigger signal to account for cardiac

motion, ECG signal was logged and synchronized with data acquisition for retrospective data selection. Previous studies have proposed several approaches for cardiac self-navigation using radial or spiral trajectories (22,23). Thus, cardiac self-navigation, besides respiratory self-navigation, could be also investigated in future studies to achieve free-breathing, ECG-free 3D myocardial T1 mapping.

T1 mapping at systole has special diagnostic value when the diastolic T1 map cannot be reliably obtained, such as in patients with thin myocardium, where partial volume effects may corrupt myocardial T1 estimation, and in patients suffering from frequent arrhythmias, where the diastolic onset and duration are changing (28,29). In this study, systolic T1 maps were reconstructed along with diastolic T1 maps for each subject. The AHA segment analysis showed good spatial uniformity of the myocardial T1 values measured across the left ventricle in both diastole and systole. In general, the systolic myocardium T1 was comparable to the diastolic myocardium T1. The shorter T1 in the inferoseptal segment of the basal slice and inferior segments of the mid and apical slices may be explained by increased myocardial thickness and thus reduced partial volume effects from blood during systole compared to diastole (29). The acquisition window for T1 mapping was set to about 186 ms, which was adequate for diastole, but may not be optimal for systole. In spite of this, radial data acquisition is less sensitive to motion than Cartesian sampling, and no obvious motion artefacts were observed in the systolic T1 maps.

Systolic and diastolic T1 maps were reconstructed for each subject separately in our experiments. Instead of separate reconstruction for each cardiac phase, cardiac-resolved T1 maps can be reconstructed simultaneously, by which additional redundancy along cardiac phases can be exploited and improved reconstruction performance can be expected at the expenses of memory requirement and computational times. Furthermore, 3D cardiac cine reconstruction from the free-running sequence should be also possible. This could be done by sorting the respiration motion compensated k-space data with a small temporal window along the cardiac phase (e.g., 50ms) and a large temporal window along contrast. After binning, the undersampled k-space data of different cardiac phases could be reconstructed simultaneously for example by adding a total variation constraint along the cardiac phase direction (31) to the reconstruction Equation [2]. This approach will be investigated in future studies.

SPGR readout with low flip angle instead of balanced steady-state free precession (bSSFP) readout was used in the proposed sequence. Although bSSFP readout may have SNR benefits, the low flip angle SPGR readout is less sensitive to B1 and B0 field inhomogeneities which

will influence T1 estimation and may cause banding artefacts in the image. The proposed technique was investigated at 1.5T in this study, but has potential to be extended to 3T. Furthermore, benefits of higher SNR, and thus shortened scan time or improved spatial resolution can be expected at 3T.

Several limitations of the proposed technique need to be mentioned. Firstly, the proposed T1 mapping technique cannot estimate T1 of flowing blood accurately. This is because the signal model used for T1 mapping assumes that the tissue of interest is static and experiences all the inversion and excitation pulses in the sequence, which may not be true for flowing blood. When measurement of myocardial extracellular volume is needed, estimation of blood T1 could be performed using a free-breathing rapid low spatial resolution (enough to only define a region of interest within the blood pool) T1 mapping sequence acquired in a mid-ventricular slice. Secondly, in this study the proposed technique was only tested for native myocardial T1 mapping. However, post-contrast myocardial T1 mapping using this technique should be also feasible. Furthermore, considering the reduced T1 after contrast injection, shorter IRTR could be adopted and shorter scan duration can be expected. Thirdly, in the free-running sequence with retrospective binning, although inter-bin respiratory and cardiac motion has been carefully addressed, compared with breath-hold images, there may still be some remaining intra-bin respiratory motion and cardiac motion that result in some blurring of the reconstructed images. Future studies will investigate the performance of the proposed sequence in a cohort of patients with cardiovascular disease. Lastly, the current implementation of HD-PROST reconstruction is suboptimal and it takes about 3 hours to reconstruct a whole heart 3D T1 map. GPU implementation will be investigated in the future for the non-uniform Fourier Transform (32) and the patch-based denoising process to accelerate the reconstruction.

CONCLUSIONS

In this study, a free-running 3D myocardial T1 mapping technique with whole heart coverage and high isotropic spatial resolution is proposed. 3D T1 mapping was shown to have good accuracy and precision in comparison to reference sequence in phantom and conventional T1 mapping methods in in vivo experiments. Based on retrospective data selection and combined dictionary-based low-rank inversion and patch-based reconstruction, high resolution 3D T1 maps could be obtained for different cardiac phases. Future studies will investigate the clinical value of the proposed technique.

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REFERENCES

1. Patel AR, Kramer CM. Role of Cardiac Magnetic Resonance in the Diagnosis and Prognosis of Nonischemic Cardiomyopathy. *JACC Cardiovasc Imaging* 2017;10(10 Pt A):1180-1193.
2. Hamlin SA, Henry TS, Little BP, Lerakis S, Stillman AE. Mapping the future of cardiac MR imaging: case-based review of T1 and T2 mapping techniques. *Radiographics* 2014;34(6):1594-1611.
3. Schelbert EB, Messroghli DR. State of the Art: Clinical Applications of Cardiac T1 Mapping. *Radiology* 2016;278(3):658-676.
4. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017;19(1):75.
5. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Choudhury RP, Friedrich MG, Robson MD, Neubauer S. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2012;14:42.
6. Bull S, White SK, Piechnik SK, Flett AS, Ferreira VM, Loudon M, Francis JM, Karamitsos TD, Prendergast BD, Robson MD, Neubauer S, Moon JC, Myerson SG. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart* 2013;99(13):932-937.
7. Karamitsos TD, Piechnik SK, Banyersad SM, Fontana M, Ntusi NB, Ferreira VM, Whelan CJ, Myerson SG, Robson MD, Hawkins PN, Neubauer S, Moon JC. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2013;6(4):488-497.
8. Sado DM, White SK, Piechnik SK, Banyersad SM, Treibel T, Captur G, Fontana M, Maestrini V, Flett AS, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Neubauer S, Elliott PM, Moon JC. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. *Circ Cardiovasc Imaging* 2013;6(3):392-398.
9. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson* 2016;18(1):89.
10. Messroghli DR, Radjenovic A, Kozierke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. *Magn Reson Med* 2004;52(1):141-146.
11. Chow K, Flewitt JA, Green JD, Pagano JJ, Friedrich MG, Thompson RB. Saturation recovery single-shot acquisition (SASHA) for myocardial T(1) mapping. *Magn Reson Med* 2014;71(6):2082-2095.

12. Kellman P, Hansen MS. T1-mapping in the heart: accuracy and precision. *J Cardiovasc Magn Reson* 2014;16:2.
13. Kellman P, Chefd'hotel C, Lorenz CH, Mancini C, Arai AE, McVeigh ER. Fully automatic, retrospective enhancement of real-time acquired cardiac cine MR images using image-based navigators and respiratory motion-corrected averaging. *Magn Reson Med* 2008;59(4):771-778.
14. Nordio G, Henningsson M, Chiribiri A, Villa ADM, Schneider T, Botnar RM. 3D myocardial T-1 mapping using saturation recovery. *Journal of Magnetic Resonance Imaging* 2017;46(1):218-227.
15. Christodoulou AG, Shaw JL, Nguyen C, Yang Q, Xie Y, Wang N, Li D. Magnetic resonance multitasking for motion-resolved quantitative cardiovascular imaging. *Nat Biomed Eng* 2018;2(4):215-226.
16. Shaw JL, Yang Q, Zhou Z, Deng Z, Nguyen C, Li D, Christodoulou AG. Free-breathing, non-ECG, continuous myocardial T1 mapping with cardiovascular magnetic resonance multitasking. *Magn Reson Med* 2018.
17. Weingartner S, Akcakaya M, Roujol S, Basha T, Tschabrunn C, Berg S, Anter E, Nezafat R. Free-breathing combined three-dimensional phase sensitive late gadolinium enhancement and T1 mapping for myocardial tissue characterization. *Magn Reson Med* 2015;74(4):1032-1041.
18. Guo R, Chen Z, Wang Y, Herzka DA, Luo J, Ding H. Three-dimensional free breathing whole heart cardiovascular magnetic resonance T1 mapping at 3 T. *J Cardiovasc Magn Reson* 2018;20(1):64.
19. Chan RW, Ramsay EA, Cunningham CH, Plewes DB. Temporal Stability of Adaptive 3D Radial MRI Using Multidimensional Golden Means. *Magn Reson Med* 2009;61(2):354-363.
20. Asslander J, Cloos MA, Knoll F, Sodickson DK, Hennig J, Lattanzi R. Low rank alternating direction method of multipliers reconstruction for MR fingerprinting. *Magn Reson Med* 2018;79(1):83-96.
21. Bustin A, Cruz G, Jaubert O, Lopez K, Botnar RM, Prieto C. High-dimensionality undersampled patch-based reconstruction (HD-PROST) for accelerated multi-contrast magnetic resonance imaging. *Magn Reson Med* 2019;(Epub).
22. Bonanno G, Hays AG, Weiss RG, Schar M. Self-gated golden angle spiral cine MRI for coronary endothelial function assessment. *Magn Reson Med* 2018;80(2):560-570.
23. Larson AC, White RD, Laub G, McVeigh ER, Li D, Simonetti OP. Self-gated cardiac cine MRI. *Magn Reson Med* 2004;51(1):93-102.
24. Qi H, Sun J, Qiao H, Chen S, Zhou Z, Pan X, Wang Y, Zhao X, Li R, Yuan C, Chen H. Carotid Intraplaque Hemorrhage Imaging with Quantitative Vessel Wall T1 Mapping: Technical Development and Initial Experience. *Radiology* 2018;287(1):276-284.
25. Qi H, Sun J, Qiao H, Zhao X, Guo R, Balu N, Yuan C, Chen H. Simultaneous T1 and T2 mapping of the carotid plaque (SIMPLE) with T2 and inversion recovery prepared 3D radial imaging. *Magn Reson Med* 2018;80(6):2598-2608.
26. Captur G, Gatehouse P, Keenan KE, Heslinga FG, Bruehl R, Prothmann M, Graves MJ, Eames RJ, Torlasco C, Benedetti G, Donovan J, Ittermann B, Boubertakh R, Bathgate A, Royet C, Pang W, Nezafat R, Salerno M, Kellman P, Moon JC. A medical device-grade T1 and ECV phantom for global T1 mapping quality assurance-the T1 Mapping and ECV Standardization in cardiovascular magnetic resonance (TIMES) program. *J Cardiovasc Magn Reson* 2016;18(1):58.
27. Messroghli DR, Greiser A, Frohlich M, Dietz R, Schulz-Menger J. Optimization and validation of a fully-integrated pulse sequence for modified look-locker inversion-recovery (MOLLI) T1 mapping of the heart. *J Magn Reson Imaging* 2007;26(4):1081-1086.
28. Ferreira VM, Wijesurendra RS, Liu A, Greiser A, Casadei B, Robson MD, Neubauer S, Piechnik SK. Systolic ShMOLLI myocardial T1-mapping for improved robustness to partial-volume effects and applications in tachyarrhythmias. *J Cardiovasc Magn Reson* 2015;17:77.
29. Messner NM, Budjan J, Lossnitzer D, Papavassiliu T, Schad LR, Weingartner S, Zollner FG. Saturation-Recovery Myocardial T1-Mapping during Systole: Accurate and Robust Quantification in the Presence of Arrhythmia. *Sci Rep* 2018;8(1):5251.

30. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS, American Heart Association Writing Group on Myocardial S, Registration for Cardiac I. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *J Nucl Cardiol* 2002;9(2):240-245.
31. Feng L, Coppo S, Piccini D, Yerly J, Lim RP, Masci PG, Stuber M, Sodickson DK, Otazo R. 5D whole-heart sparse MRI. *Magn Reson Med* 2018;79(2):826-838.
32. Knoll F, Schwarzl A, Diwoky C, DK. S. gpuNUFFT - An Open-Source GPU Library for 3D Gridding with Direct Matlab Interface. *ISMRM* 2014;p 4294.

FIG. 1 A: Schematic diagram of the proposed free-running myocardial 3D T1 mapping sequence. After inversion recovery (IR) preparation, spoiled gradient echo (SPGR) readout with low flip angle (θ) was performed using 3D golden angle radial trajectory. T_{gap} is the time between the IR pulse and the first excitation and T_{ex} is the time interval between the last excitation in the SPGR readout and the next IR pulse. IRTR is the IR repetition time. B: Data sorting process for reconstruction of multiple T1 contrasts for a given cardiac phase, which includes three steps: 1D respiratory motion estimation from k-space center of all radial spokes and cardiac motion extraction from ECG log; respiratory motion correction of k-space using motion parameters estimated by 3D translational image registration of respiratory bin images at diastole; binning the respiratory motion corrected k-space into different T1 contrasts for a given cardiac phase.

FIG. 2 A: The 5 independent components (IC) extracted from the k-space center of all spokes using independent component analysis. B: The spectral power of the signal components in A. C: The IC (IC 4) with highest spectral power in the respiratory frequency range (0.1-0.5Hz) is selected and band-pass filtered and compared with respiration bellow. D: Example of low-resolution self-navigated images of 5 respiratory bins from intermediate reconstruction for 3D translational respiratory motion estimation. Setting bin 5 as the reference, its difference with other respiratory bins are shown in the second row to demonstrate the extent of respiration-induced motion of the heart in this subject. The difference images are demonstrated with the same gray level range.

FIG. 3 A: The singular values obtained by singular value decomposition of the dictionary simulated according to the imaging and reconstruction parameters of the proposed 3D T1 mapping technique using Bloch simulation. B: The singular value images corresponding to the three largest singular values in A reconstructed by direct back projection and HD-PROST (high-dimensionality 3D patch-based undersampled reconstruction) algorithm.

FIG. 4 A, B: Phantom T1 maps of 2D inversion recovery spin echo (2D IR-SE) and the proposed 3D T1 mapping approach. C: Linear correlation of phantom T1 estimation with the proposed 3D method in comparison with reference 2D IR-SE sequence. D: Bland-Altman plot showing the difference between the two methods and their average. The grey solid line indicates the mean difference, and the grey dotted lines indicate the 95% confidence intervals of limits of agreement.

FIG. 5 Proposed 3D T1 mapping technique at diastolic cardiac phase for a representative healthy subject. Eight short-axis slices, from apex to base of the left ventricle and the reformatted long-axis view are shown. Uniform T1 distribution across the myocardium can be observed.

FIG. 6 Short-axis 2D MOLLI (modified Look-Locker inversion recovery), 2D SASHA (saturation recovery single-shot acquisition) and the proposed 3D T1 mapping results at diastolic cardiac phase for two healthy subjects. Long-axis view is also included for the proposed 3D T1 mapping technique.

FIG. 7 A: Mean septum T1 values of all nine healthy subjects measured with 2D MOLLI (modified Look-Locker inversion recovery), 2D SASHA (saturation recovery single-shot acquisition) and the proposed free-running 3D T1 mapping technique. B: Standard deviations of the septal T1 measurements from all the subjects for the three methods. The mean \pm SD (standard deviation) across all the subjects are shown on top of each method (** $P < 0.01$).

FIG. 8 Representative diastolic and systolic T1 maps of basal, mid and apical short-axis views using the proposed 3D T1 mapping sequence from two healthy subjects (A, B). Uniform myocardial T1 distribution can be observed on the T1 maps, both in diastole and systole.

FIG. 9 A: AHA bull's eye plots showing the myocardium T1 distribution across the left ventricle at diastole and systole with the proposed free-running 3D T1 mapping technique. The mean values obtained by averaging across all the subjects are shown in each segment (* $P < 0.05$, ** $P < 0.01$). B: Box plots showing the median, 25 and 75 percentiles, and range of the diastolic and systolic T1 in each AHA segment. (A: anterior; AS: anteroseptal; IS: inferoseptal; I: inferior; IL: inferolateral; AL: anterolateral; S: septal; L: lateral).

Table 1 The P value of paired t-test comparison of diastolic and systolic T1 values in each AHA segment with the proposed free-running 3D T1 mapping technique

	A	S		I	L	
		AS	IS		IL	AL
Base	0.30	0.06	0.02*	0.10	0.57	0.73
Middle	0.57	0.25	0.13	<0.01**	>0.99	0.36
Apex	0.25	0.20		<0.01**	0.13	

* $P < 0.05$; ** $P < 0.01$; A: anterior; AS: anteroseptal; IS: inferoseptal; I: inferior; IL: inferolateral; AL: anterolateral; S: septal; L: lateral